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ZA INTELEKTUALNO LAS... LJUBLJANA, KOTNIKOVA 6

ZAHTEVA ZA PODELITEV PATENTA

1. Naslov za obveščanje:

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Potrdilo o prejemu prijave
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Registrska številka:

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5. Naziv izuma:
Farmacevtska formulacija olanzapina

6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

7. Dodatne zahteve:
☐ prijava je za patent s skrajšanim trajanjem
☐ predhodna objava patenta po preteku ____ mesecev
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8. Izjava:
☐ izjava o skupnem predstavniku:

9. Priloge:
☒ opis izuma, ki ima 9 strani
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Priimek in ime ter podpis prijavitelja
Mihael Florjanič

Obrazec SIPO P-1

Pharmaceutical formulation of olanzapine

The present invention relates to pharmaceutical composition containing a homogeneous mixture of (a) 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b][1,5]benzodiazepine, in the following referred to by its generic name olanzapine, or a pharmaceutically acceptable salt thereof, (b) a monosaccharide and/or oligosaccharide, and (c) a polysaccharide.

Technical field

Olanzapine is an antagonist of dopamine at D-1 and D-2 receptors, and in addition has antimuscarinic anti-cholinergic properties and antagonist activities at 5HT-2 receptor sites. It also has antagonist activity at noradrenergic α-receptors. The compound is a potential neuroleptic with relaxant, anxiolitic or anti-emetic properties, and is useful in treating psychotic conditions such as schizophrenia, schizophreniform diseases and acute mania. At lower doses the compound is indicated for use in the treatment of mild anxiety states.

Technical problem

Due to moisture sensitive, metastable nature of olanzapine the formulation presently on the market requires several steps in technological preparation such as granulation, compression, sub coating and coating in order to assure protection of the active substance from moisture and light. Such a technological process is technologically and economically demanding therefore exists a need to develop a stable formulation obtained by technologically and economically more acceptable process.

According to present invention there is provided a formulation with high stability absent from phenomena of undesired discoloration or poor dose uniformity. The formulations of the present invention can be prepared by a simple technological process, such as direct compression.

State of the art

In EP 454436 B1 it is reported that pharmaceutical compositions of olanzapine can be prepared by using conventional techniques. The active ingredient can be mixed with carrier such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl and propyl-hydroxy

benzoate, talc, magnesium stearate or mineral oil. In a specific example is given a formulation prepared by granulation and compressing containing magnesium stearate, microcrystalline cellulose, povidone and starch. Depending on the method of administration, the compositions may be formulated as tablets, capsules, injection solutions for parenteral use, suspensions or elixirs for oral use or suppositories.

EP 733367 B1 relates to a stable solid oral formulation comprising olanzapine intimately mixed with a bulking agent, binder, disintegrant, a dry binder and a lubricant wherein such solid oral formulation is coated with polymer. Coating with certain polymers is said to provide uniformity, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation. Ambient conditions, elevated temperatures and moist environment exacerbate the problem of discoloration which is believed to be particularly disturbing when a tablet formulation is administered to a psychotic patient. Process for preparation of the formulation comprises the steps of wet granulation, drying, blending with additional excipients and compression. The obtained cores are first sub-coated with HPMC in order to avoid direct contact of active ingredient with polyethylene glycol and further coated with coated suspension. In the description it is pointed out that olanzapine may form an undesired crystal form in the presence of certain solvents and excipients, therefore it is desired to prepare the formulation using a method which does not require dissolution of olanzapine substance. They believe that dry blend direct compression process or dry granulated process for preparing solid oral formulations create a greater chance that poor dose uniformity will occur. In light of the potent nature of olanzapine, consistent dose uniformity is imperative therefore they used high shear aqueous wet granulation with fluid bed drying as the most effective method for preparing pharmaceutically elegant, stable, oral olanzapine formulations. Despite the fact that presence of solvents can cause the undesirable conversions they could not avoid the use of wet granulation, this problem has been successfully solved by the present invention.

EP 830858 A1 relates to formulation containing coated active ingredient. Coating provides uniform, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation. It is stated that known formulation described in US 5229382, counterpart to EP 454436, shows the tendency of olanzapine to undesirably discolor. They stated that

olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends.

In WO 98/11897 is disclosed a formulation of olanzapine in fixed combination with fluoxetine comprising microcrystalline cellulose, silicone dioxide and stearic acid. The components are blended and compressed to form tablets.

Description of the invention

According to present invention it is disclosed a pharmaceutical formulation, comprising (a) as active ingredient 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b][1,5]benzodiazepine or a pharmaceutically acceptable salt thereof, (b) a monosaccharide and/or oligosaccharide, and (c) a polysaccharide. Components (b) and (c) serve as a diluent for the active ingredient. The formulations of the present invention preferably also contain a binder, a disintegrating agent and a lubricant. The formulations of the present invention preferably have the form of tablets. The term "tablet" as used herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes. Uncoated tablets are particularly preferred. According to a preferred embodiment of the present invention the tablets are prepared by direct compression. During our development we have found that discoloration phenomenon is probably caused by formation of olanzapine hydrates, which have less intensive colour as olanzapin. In order to prevent formation of hydrates the process for the manufacture of pharmaceutical formulation should be performed without using solvents. It was surprisingly found by the present inventors that stable pharmaceutical formulations comprising olanzapine as the active ingredient which do not show undesired discoloration and which have excellent dose uniformity can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogeneously mixed with certain excipients and then subjected to direct compression. Direct compression is preferably performed in the absence of solvent. In view of the fact that the excipients used by the present inventors are commonly used for manufacturing tablets the finding that they allow the production of stable olanzapine formulations without need for a coating or wet granulation was totally unexpected.

The most obvious advantage of direct compression is economy. Savings can occur in a number of areas, including reduced processing time and thus reduced labour costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption of power.
The most significant advantage in term of tablet quality is that of processing without the need for moisture and heat which is inherent in most wet granulation procedures, and the avoidance of high compaction pressures involved in producing tablets by slugging or roll compaction. Such as process can improve the stability of tablet formulations which contain to the moisture and temperature sensitive drug.

It has been surprisingly found that the use of particular diluents, i.e. a mixture of components (a) and (b), makes direct compression process to be applicable for the manufacture of olanzapine tablets demonstrating colour stability and dose uniformity.

The term "direct compression" refers to a process wherein the various compounds of the tablet are mixed together, optionally milled, sieved and then compressed into tablets. Mixing of the compounds may be achieved in one or more steps. For instance, the active ingredient may first be mixed with a binder and this mixture can than be combined with a mixture of the other ingredients. The whole process is preferably performed in the absence of solvent.

Suitable salts are for instance disclosed in EP 0 454 436 B1. If not specified otherwise all percentages herein are by weight and based on the total weight of the tablet. The active ingredient is evenly distributed in a matrix formed by the other ingredients of the formulation. The tablets do not have a layered structure and, as noted above, are preferably uncoated.
The formulations of the present invention may contain anhydrous forms of olanzapine which are disclosed e.g. in EP 0 733 635 B1 therein designated as Form I and Form II; in US 6348458 therein designated as Form III, Form IV, Form V; in US 2002/0086993 A1 thereindesignated as form X. Olanzapine used may also be in polymorphic form A of olanzapine and olanzapine solvates, such as acetonitrile/methylene chloride/water, acetonitrile/water mixed solvates, 2-propanol solvate, methylene chloride solvate IA, methylene chloride solvate IB as disclosed in pending patent application SI 200200175. Also useful are hydrates of olanzapine which are disclosed e.g. in EP 831098 B1 therein designated

as forms B, D, E; in WO 02/18390 therein designated as monohydrate I and dihydrate I. Also useful are solvates disclosed in EP 733634 therein designated as mono methanol solvate, mono ethanol solvate, mono 1-propanol solvate.

Olanzapine is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from 0.25 to 50 mg, preferably 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. A preferred tablet of the invention thus comprises 0.25 to 50 mg, preferably 1 to 30 mg and in particular 1 to 20 mg olanzapine (calculated as the free anhydrous base).

The preferred weight of the tablets is 50 to 1000mg, most preferably 100 to 500mg.

The formulations of the invention preferably comprise from 40 to 80 weight %, more preferably from 45 to 75 weight % and most preferably from 50 to 70 weight % of component (b); 10 to 40 weight %, more preferably from 15 to 30 weight % and most preferably from 15 to 25 weight % of component (c). According to a preferred embodiment the tablets of the invention comprise olanzapine or a pharmaceutically acceptable salt thereof as the only pharmaceutically active ingredient.

Component (b) is a monosaccharide, oligosaccharide or a mixture of monosaccharide and oligosaccharide. The terms "monosaccharide" and "oligosaccharide" are intended to also cover derivatives of monosaccharides and oligosaccharides, in particular the reduced and oxidised forms thereof, such as sugar alcohols, e.g. sorbitol, monitol, lactitol. Oligosaccharides are compounds comprising 2 to 6, preferably 2 or 3 monosaccharide residues. Carbohydrates comprising more than 6 monosaccharide residues are referred to as polysaccharides.

Component (b) is preferably selected from the group consisting of lactose, sucrose, dextrose, sorbitol, manitol, lactitol, and mixtures thereof. According to an especially preferred embodiment coponent (b) is lactose, more preferably alpha-lactose and most preferabyl alpha-

lactose monohydrate (Ph. EUR./USP-NF/JP). These compounds may be used in spray-dried form.

Component (c) is a polysaccharide, preferably a polysaccharide comprising from 200 to 10,000 monosaccharide residues, preferably 500 to 10,000 monosaccharide residues, preferabyl glucose residues. Component (c) is preferably selected from the group consisting of starch, such as pregelatinized starch, cellulose and mixtures thereof.

According to a particularly preferred embodiment component (c) is cellulose powder (Ph. Eur.). Although other forms of cellulose may be used, these forms are usually not preferred. Microcrystalline cellulose for instance is relatively hygroscopic which may adversely affect the stability of the finished product. The same is true for modified starch. Tablets which do not contain microcrystalline cellulose are preferred.

Components (b) and (c) are preferably used in a ratio of 20 to 30 weight %, preferably 25 weight % of component (c) and 70 to 80 weight %, preferably 75 weight % of component (b), based on the total weight of components (b) and (c). Particularly preferred is a mixture of 75 weight % of alpha-lactose monohydrate and 25 weight % cellulose powder (dry matter).

Components (b) and (c) are preferably used in a premixed form, obtained for instance by mixing (b) and (c) and optionally water and spray-drying this mixture. The particles size distribution of components (b) and (c) or the premixed form of components (b) and (c) is preferably as follows: < 100 µm: max. 25 %; < 200 µm: max. 65 %; < 400 µm: min. 98 %, determined by an air jet sieve. For the production of tablets of the present invention it is preferred that the particle size of all excipients is of the same degree.

A premixed form of 75 weight % alpha-lactose monohydrate and 25 weight % cellulose powder which can be used for preparing the tablets of the invention is sold as Cellactose®80 by Meggle GmbH, Wasserburg, Germany.

In the tablets of the invention components (b) and (c) serve as diluents. In addition to components (b) and (c) the tablets may comprise other diluents, such as calcium phosphate d.c. grade and povidone (PVP), such as cross-linked PVP.

The main benefits of the combined use of components (b) and (c) are high content uniformity due to low segregation tendency, excellent compactibility offers possibilities for poorly compressible actives, stable consistency of lactose/cellulose system leading to constant tablet hardness, good flowability providing high weight consistency at various tableting speeds.

The pharmaceutical formulations of the present invention may contain additional ingredients selected from a wide variety of excipients known in the pharmaceutical formulation art, such as disentegrants, binders, lubricants, and glidants.

Suitable disintegrates are e.g. maize starch, sodium starch glycolate, crospovidone, carboxymethylcellulose sodium, croscarmelose sodium.
Suitable binders are starches, cellulose, PVP. Cellactose has simultaneously a role of binder and diluent and thus the use of an additional binder can be avoided if Cellactose is used in the tablets of the invention. Lubricant and glidants e.g. silica, colloidal anhydrous are used in the formulations of the invention in a usual standard way.
The amounts of excipients used in the formulation are for diluent from 20-90%, preferably from 50 to 85 weight %, for disintegrant up to 15%, preferably up to 10 weight %, binder of 5-20%, preferably 5 to 15 weight %, lubricant 0,25-5%, preferably 0.5 to 3 weight %, glidant 0,1-0,5%, preferably 0.2 to 0.5 weight %.
In the preferred embodiment the formulation of the invention comprises 70-90% by weight of a premixed form of components (b) and (c) as defined above, 8-12% by weight of binder selected from pregelatinized starch, 3-10% by weight of disintegrant selected from maize starch, 0,3%-2 by weight of lubricant and 0,2-0,4% by weight of glidant.

In the state of the art it is stressed that due to a potent nature of olanzapine, consistent dose uniformity is imperative, and that such uniformity is hardly obtained by direct compression. We have unexpectedly found out that despite the low dose of the active compound in the tablet according to present invention excellent dose uniformity is obtained which is shown by

analytical result of content uniformity test where relative standard deviation (RDS) is of 0,7-1%. This is attributable to good flowability of compression mixture which therefore provides for low weight variation, RSD is equal or less than 0,8%, at various compression speeds.

The uniformity of the tablets is determined according to standard procedures as described in Pharmaceutical Dosage Forms, Second Edition, Volume 2, H.A. Lieberman, L. Lachman, J.B. Schwartz (Editors), Marcel Dekker, Inc,. New York and Bases, pages 321 to 325.

The optimisation of tablet formulation is closely related to the intention to have the process of tablet manufacture as simple as possible and to avoid laborious operations that may unnecessary expose a processed material with a heat or increased moisture. According to present invention we avoided the use of the solvents for granulation which may cause conversion to different polymorphic forms or hydrates and therefore avoid the moisture conditions under which olanzapine is not stable, additionally any drying is required during the process therefore the use of elevated temperatures which may cause discoloration is avoided.

The examples provided below are provided for the purposes of illustration and are not to be construed as limiting the scope of the invention.

Examples

Example 1
Referential example

Olanzapine	10.00 mg
Microcrystalline cellulose	247.00 mg
Starch pregelatinized	30.00 mg
Sodium starch glycolate	9.00 mg
Silica, colloidal anhydrous	1.00 mg
Magnesium stearate	3.00 mg

Olanzapine, starch pregelatinized and sodium starch glycolate were mixed together and milled. Microcrystalline cellulose, silica, colloidal anhydrous and magnesium stearate were sieved, blended with premixture of the drug and compressed into tablets.

Stability results at test conditions:

- (1 month, 40°C/75%RH, open air): increase in total related compounds from 0.49% to 3.40%.

Example 2

Olanzapine	10.00 mg
Cellactose	247.00 mg
Starch pregelatinized	30.00 mg
Sodium starch glycolate	9.00 mg
Silica, colloidal anhydrous	1.00 mg
Magnesium stearate	3.00 mg

Olanzapine, starch pregelatinized and sodium starch glycolate were mixed together and milled. Cellactose, silica, colloidal anhydrous and magnesium stearate were sieved and blended with premixture of the drug.The compression mixture was compressed into tablets.

Stability results at test conditions:

- (1 month, 40°C/75%RH, open air): increase in total related compounds from 0.40% to 1.63%.

Example 3

Olanzapine	10.00 mg
Cellactose	227.00 mg
Starch pregelatinized	30.00 mg
Maize starch	9.00 mg
Silica, colloidal anhydrous	1.00 mg
Magnesium stearate	3.00 mg

Olanzapine and maize starch were mixed together and milled. Cellactose, starch pregelatinized, silica, colloidal anhydrous were sieved and blended with premixture of the drug. Magnesium stearate was sieved and added to the mixture. The compression mixture was compressed into tablets.

Stability results at test conditions:

- (6 months, 40°C/75%RH, Al/OPA foil): increase in total related compounds from 0.10% to 0.35%.

Claims

1. A pharmaceutical formulation comprising a homogeneous mixture of (a) olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient, (b) a monosaccharide and/or oligosaccharide, and (c) a polysaccharide.

2. The pharmaceutical formulation of claim 1 comprising 40 to 80 weight % of component (b).

3. The pharmaceutical formulation of any one of claims 1 to 2 comprising 10 to 40 weight % polysaccharide.

4. The pharmaceutical formulation of any one of claims 1 to 3 additionally comprising (d) up to 15 weight % disintegrant.

5. The pharmaceutical formulation of any one of claims 1 to 4 additionally comprising (e) 5 to 20 weight % binder.

6. The pharmaceutical formulation of any one of claims 1 to 5 additionally comprising (f) 0.25 to 5 weight % lubricant.

7. The pharmaceutical formulation of any one of claims 1 to 6 additionally comprising (g) 0.1 to 0.5 weight % glidant.

8. The pharmaceutical formulation of any one of claims 1 to 7 wherein component (b) is selected from the group consisting of lactose, sucrose, dextrose, sorbitol, manitol, lactitol, and mixtures thereof.

9. The pharmaceutical formulation of claim 8 wherein component (b) is lactose.

10. The pharmaceutical formulation of any one of claims 1 to 9 wherein the polysaccharide is selected from the group consisting of starch, cellulose, and mixtures thereof.

11. The pharmaceutical formulation of claim 10 wherein the polysaccharide is cellulose.

12. The pharmaceutical formulation of claim 11 wherein a mixture of 20 to 30 weight % cellulose and 70 to 80 weight % lactose is used as components (b) and (c).

13. The pharmaceutical formulation of claim 12 comprising
70 to 90 weight % of a mixture of 20 to 30 weight % cellulose and 70 to 80 weight % lactose;
8 to 12 weight % binder;
3 to 10 weight % disintegrant;
0.3 to 2 weight % lubricant; and
0.2 to 0.4 weight % glidant.

14. The pharmaceutical formulation of any one of claims 1 to 13 being obtainable by direct compression.

15. The pharmaceutical formulation of any one of claims 1 to 14 comprising olanzapine as the only pharmaceutically active ingredient.

16. The pharmaceutical formulation of any one of claims 1 to 15 having the form of an uncoated tablet.

17. A process for preparing a stable pharmaceutically solid oral according to any one of claims 1 to 16 comprising combining (a) olanzapine or a pharmaceutically acceptable salt thereof with (b) a monosaccharide and/or oligosaccharide, (c) a polysaccharide and optionally one or more of components (d) to (g) followed by direct compression of the mixture into tablets in the absence of solvent.

Summary

A pharmaceutical formulation comprising a homogeneous mixture of (a) olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient, (b) a monosaccharide and/or oligosaccharide, (c) a polysaccharide and optionally further ingredients .

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*** POROCILO O SPREJEMU ***
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